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Original Research Article

The efficacy of alpha-lipoic acid and/or gabapentin on the oxidant-antioxidant system in patients with diabetic polyneuropathy

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ABSTRACT

Background: Diabetic peripheral sensorimotor polyneuropathy is the most common complication seen in patients with diabetes mellitus (DM). Oxidant system plays a crucial role in its physiopathology. We investigated the changes in the serum levels of total antioxidant status (TAS), total oxidant status (TOS), paraoxonase-1 (PON1) and oxidative stress index (OSI) to evaluate the antioxidant efficacy of alpha lipoic acid (ALA) and/or gabapentin in patients with diabetic polyneuropathy (DPN).
Methods: Sixty-three type 2 DM patients with diabetic polyneuropathy (DPN) were enrolled in the study. Patients with DPN were divided into four groups in terms of their treatment: Group 1 consisted of treatment-naive patients; patients treated with ALA, gabapentin or combination of ALA and gabapentin comprised groups 2, 3, and 4, respectively. The patients received the medications for at least six weeks. Serum levels of TAS, TOS, PON1 and OSI were analyzed.
Results: No significant difference was observed between the groups according to the oxidative stress parameters studied.
Conclusions: The use of ALA and/or gabapentin in patients with DPN did not significantly affect the oxidative stress parameters, including TAS, TOS, PON1, and OSI.

Keywords: Alpha-lipoic acid, Diabetic polyneuropathy, Gabapentin, Paraoxonase-1, Total antioxidant status, Total oxidant status

INTRODUCTION

Diabetic polyneuropathy (DPN) is the most common complication in patients with diabetes. More than 50% of the patients with diabetes mellitus (DM), experience diabetic polyneuropathy.[1]

Among many mechanisms proposed for its pathophysiology, the most widely accepted one is the microvascular damage caused by the formation of reactive oxygen species (ROS) which leads to DPN.[2]

The aim of the treatment of DPN is to prevent neurologic damage and control the symptoms.[3] Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, antiepileptics, opioids and mexiletine have been proposed for the symptomatic treatment of DPN.[4,5] Increase in ROS and oxidative stress plays an important role for the development of DPN.[6-10] Thus, antioxidant drugs such as alpha- lipoic acid (ALA) can be used for the treatment of DPN.[6] Neuroprotective and also pain-relieving effects of ALA therapy have been reported in the literature.[1,2]

Gabapentin, a gamma aminobutyric acid (GABA) analog, has an important role in the treatment of neuropathic pain, epilepsy and spasticity.[11] In addition, the effects of gabapentin on the neuroprotection and oxidative stress have also been reported.[12]

Oxidative stress has been defined as an imbalance between oxidant and antioxidant systems, occurring when the oxidant capacity exceeds the antioxidant capacity.[13-15] Total antioxidant status (TAS), total oxidant status (TOS), paraoxonase-1 (PON1), the oxidative stress index (OSI) are parameters used for representing oxidative stress. TAS induced by hydroxyl radicals has antioxidative effect against the potent free radical reactions.[16] TOS is related to the total amount of oxidant molecules. The ratio of TOS to TAS level is defined as OSI.[7] PON1 reduces oxidative stress in lipoproteins, macrophages and the atherosclerotic lesions.[17,18] Serum PON1 activities are effected by systemic lipid peroxidation stress and atherogenesis.[19] Atherosclerosis is one of the significant factors causing DPN.

In previous studies conducted to define oxidative status in type 2 diabetics with or without polyneuropathy, increased TOS and OSI, while decreased TAS levels were reported regardless of the presence of concomitant neuropathy.[7] However, levels of TAS, TOS, PON1 and OSI have not been studied in DPN patients receiving drug treatments. Besides the effectiveness of ALA and gabapentin in DPN is yet need to be clarified.

In this study, we investigated the effects of ALA and/or gabapentin on serum levels of TAS, TOS, PON1 and OSI to interpret their effects on oxidative stress in patients with diabetic polyneuropathy.

METHODS

Type 2 DM patients with a disease history of DPN more than 5 years based on clinical and electrophysiological findings were included in this study.[20] The study was conducted in line with World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects, and informed consent of the patients was obtained.

The study was approved by the local ethics committee. Patients receiving antioxidant drugs such as vitamin A, vitamin E, vitamin C, zinc, selenium, N-acetyl cysteine (NAC); neurotoxic medications such as chemotherapeutics; and also patients having endocrine and metabolic diseases that might cause peripheral polyneuropathy such as renal failure, folate deficiency, vitamin B12 deficiency, infections and peripheral vessel disease and also those with a history of cerebrovascular events, myocardial infarction, lumbosacral or cervical pathologies, cancer, and rheumatic disease were excluded from the study.

Patients meeting the inclusion and exclusion criteria mentioned above were randomly divided into 4 groups according to the treatment they received as follows: Group 1 was comprised of treatment-naive patients. Group 2, 3 and 4 were comprised of patients on treatment for at least 6 weeks receiving ALA 600 mg daily, gabapentin 900-3200 mg daily, combination of ALA and gabapentin, respectively.

For biochemical analyses venous blood samples collected in the morning after an overnight fasting were immediately centrifuged at 1500 *g*, and +4^{0}C for 10 minutes.

The serums of the blood samples were pipetted into Eppendorf tubes and kept in the deep freezer at -80^{0}C until the analysis. Measurements of the serum levels of TAS and TOS were performed using the automated measurement method developed by Erel.[14,15] PON1 activity was studied using the Eckerson method.[21] The reagents were supplied by Rel Assay Diagnostics, Mega Tip, Gaziantep, Turkey. OSI was calculated as the ratio of TOS to TAS according to following formula.[14,15] (OSI= [TOS (μmolH_2O_2 Eq/L)/TAS (mmol Trolox Eq/L)] × 100).

Statistical analysis was performed using SPSS 15.0 (Chi., IL., USA) software. Descriptive statistics were expressed as the median (min-max), frequency and percentage. Intergroup evaluation was carried out using Kruskal-Wallis test. Values of $p<0.05$ were considered statistically significant.

RESULTS

A total of 63 patients (39 females) with the diagnosis of DPN were included in the study. Median age was 59 (range: 29-80) years and the distribution according to the groups are summarized in Table 1.

Table 1: Patients characteristics in the four groups recruited according to the treatments.

	Gabapentin	ALA	Gabapentin+ALA	Control	Total
Patient numbers	19	14	6	24	63
Age (year) median (min-max)	56 (31-70)	58 (29-74)	60 (35-77)	57 (27-80)	56 (29-80)
Gender (male/female)	8/11	4/10	4/2	8/16	24/39

ALA: Alpha lipoic acid

Table 2: The effects of gabapentin and/or alpha lipoic acid usage on oxidative stress parameters in patients with diabetic polyneuropathy (median (min-max)).

	Gabapentin	ALA	Gabapentin+ALA	Control	*P$*
TAS*	2.26 (1.65-3.89)	2.03 (1.38-2.82)	1.87 (1.46-2.30)	1.96 (1.49-2.94)	0.155
TOS**	8.39 (3.22-27.30)	6.11 (3.27-12.13)	6.30 (5.12-8.95)	7.02 (2.64-30.31)	0.704
PON1***	173.00 (43-262)	107.50 (25-316)	143.00 (132-166)	135.50 (23-259)	0.913
OSI	0.38 (0.14-1.06)	0.29 (0.16-0.62)	0.38 (0.22-0.47)	0.36 (0.13-1.53)	0.824

*mmol/L Trolox Eq/L **µmol/LH_2O_2Eq/L *** U/L, $Kruskal-Wallis

ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total oxidant status, PON1: Paraoxonase, OSI: Oxidative stress index

No statistically significant difference was found among the four treatment groups in terms of oxidative stress parameters including TAS, TOS, PON1 and OSI (p>0,05; Table 2).

DISCUSSION

We studied the effects of ALA and/or gabapentin on oxidative stress parameters including TAS, TOS, PON1 and OSI in patients with DPN. As a result we could not find any significant difference among these parameters in patients receiving ALA and/or gabapentin treatments.

The most widely accepted opinion in pathophysiology of DPN is the microvascular damage resulting from the formation of reactive oxygen species.[2] Oxidative stress down-regulates Na-K-ATPase activity and leads to nerve ischemia.[6] In hyperglycemia; increase in sorbitol, decrease in myo-inositol, activation of C-protein kinase and storage of immune-complex may lead to the development of DPN.[22-24] In diabetics; inhibition of aldose reductase is achieved by the control of serum glucose; resulting in decrease in the production of sorbitol and ROS.[25,26]

Antioxidants may be administered in the treatment of DPN since the oxidative system is effective in diabetic sensorimotor polyneuropathy.[6]

Among these therapies, with its ameliorating effects on pain, ALA is the most promising drug as a prophylaxis in DPN, ALA is a fat and water-soluble sulfur-containing antioxidant.[1,2,6,22]

Having anti-inflammatory, antioxidant, cytoprotective and neuroprotective properties, ALA contributes to the control of neuropathic pain with its effects on the underlying pathophysiologic mechanisms of diabetic sensorimotor polyneuropathy.[1]

In the previous studies conducted to define oxidative status in type 2 diabetics with and without polyneuropathy, increased levels of TOS and OSI, but lower levels of TAS were found regardless of the presence of neuropathy.[7] This study is the first one investigating the PON1 and OSI in patients receiving medications for DPN.

The effects of ALA on oxidative stress have been investigated in several different diseases in recent years. Since oxidative stress is an important risk factor for cardiovascular disease in haemodialysis patients, only increase in superoxide dismutase (SOD) levels was found to be statistically significant in the study investigating the effect of ALA on antioxidant enzymes such as SOD, catalase (CAT) and glutathione peroxidase (GPx).[27] Kolahi et al, investigated the effects of oral ALA on lipid peroxidation and antioxidant biomarkers in patients with rheumatoid arthritis (RA).

They reported that when the total antioxidant capacity (TAC), antioxidant enzymes SOD, GPx and arylesterase (ARE) activities and malondialdehyde (MDA)] were examined in patients given daily doses of 1200 mg ALA or placebo for eight weeks. A significant decrease in serum TAC was observed, but these changes in the ALA-treated group were not statistically significant compared to the group receiving the placebo. In addition, in the same study, statistically significant intra-, and intergroup differences in SOD and GPx levels were not detected.

As a result, ALA treatment did not affect the oxidative status in RA patients.[28] The study of Kolahi et al supports our study and reports that ALA does not affect the oxidative status. However, they also emphasized the need to conduct larger scale studies. We also think that it is necessary to make evaluations with groups containing greater number of patients. Gabapentin is used in the treatment of neuropathic pain, epilepsy and spasticity.[11] Although gabapentin is known to exert multiple effects, their mechanisms of action remain unclear.[29] It increases GABA content in the neuronal tissue. Cerebroprotective effects of gabapentin may be associated with blockade of Ca++ channel and inhibition of nitric oxide.[29] Rehling observed the neuroprotective effects of gabapentin in the hippocampus of rats.[30] Coderne et al, emphasized the fact that excitatory amino acids are inhibited in the dorsal horn of the spinal cord with gabapentin.[31] In their in vitro studies, Rothstein and Kuncl demonstrated that neural cell death was prevented by gabapentin therapy.[32] Brito et al reported that gabapentin has anti-inflammatory effects and reduces the levels of inflammatory parameters.[33]

There are a couple of limitations in our study such as the small number of patients, variable treatment periods, and different drug dosages.

CONCLUSION

In our study, we investigated parameters such as TAS, TOS, PON1 and OSI that are important in evaluating oxidative stress in patients with DPN receiving ALA and/ or gabapentin. It was shown that the use of ALA and/or gabapentin has no significant effect on these parameters. For evaluating more detail the efficacy of the treatments on DPN, there is a need for further comparative studies including the analyzes of several other molecules such as SOD, GPx, ARE and MDA indicating oxidative stress; with a larger number of patients.

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